REMARKS

Reconsideration and allowance of the subject application in view of the foregoing amendments and the following remarks is respectfully requested.

Applicant notes with appreciation that claims 50 and 70 have been found allowable.

Claims 14-17, 37-40, and 58 have been canceled. Claims 1, 18, 21, 41, 43, 47-49, 54-56, and 59-64 have been amended and claims 2-13, 19-20, 22-36, 42, 44-46, 50-53, 57, and 65-70 are as originally presented. No new claims have been added. Upon entry of this amendment, claims 1-13, 18-36, 41-57, and 59-70 are left pending. No new matter has been added.

Response to Election/Restriction

In response to the restriction requirement claims 14-17 and 37-40 have been cancelled. Claims 1, 48, and 49 have been amended to remove non-elected subject matter. Applicant reserves the right to file a divisional to claim the non-elected subject matter.

Response to Claim Objections Under 37 CFR 1.75(c) and MPEP § 608.01(n)

Claims 18, 37-47, 54-56, and 62-64 were objected to as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Claim 55 was objected to as being in improper form because a multiple dependent claim may not depend from any other multiple dependent claim.

Claims 18, 41, 43, and 47 have been amended according to the examiner's suggestion. Claim 42 depends from amended claim 41 and claims 44-46 depend from amended claim 43.

Claims 54-56 have been amended such that they are no longer written in multiply dependent form.

Claims 62-64 have been amended such that they refer to other claims in the alternative only.

Claims 37-40 are canceled.

Response to Rejections Under 35 USC 112, First Paragraph

Claims 1-17, 19-36, 48-49, 51-53, 57-61, and 65-69 were rejected under 35 USC 112, first paragraph. It is noted with appreciation that the examiner finds the specification enabling for the compounds of Formula I or a pharmaceutically acceptable N-oxide or salt thereof. Claims 1-

17, 19-36, 48-49, 51-53, 58-61, and 66-69 were rejected because the specification does not provides enablement with respect to the preparation and/or use of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I. Claims 51-53, 57-61, and 65 were rejected because the specification does not provides enablement with respect to a method of modulating a PPAR function, a method of inhibiting the formation of adipocytes in a mammal, a method of treating a disease generally, or a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally.

Claim 58, directed towards a method of treating a disease generally, has been cancelled.

For the following reasons, it is respectfully suggested that the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I; a method of modulating a PPAR function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally; and a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury, and it is requested that the rejection be withdrawn.

Esters and Amides

In explaining the rejection of prodrugs, metabolites, esters and amides as lacking enablement, it is stated that because the definitions of various substituent groups in Formula I encompasses free acids as well as esters and amides, it is not clear what other compounds of the invention to be are intended to be the claimed prodrugs, metabolites, esters and amides of compounds of Formula I. It is further noted that the specification does not disclose esters or amides capable of providing compounds of the invention.

With respect to this portion of the rejection under 35 USC 112, first paragraph, applicant believes that the examiner has stated an argument that the terms ester and amide (and prodrug and metabolite to the extent that such derivatives include esters and amides) are not enabled because it would not be clear to a person skilled in the art what compounds are being referred to. Applicant respectfully suggests that this is not the case. An ester can be formed from an alcohol

or carboxylic acid. Likewise, an amide can be formed from an amine or carboxylic acid. As defined in claim 1, compounds of Formula I include carboxylic acids, alcohols, and amines, from which derivatives such as esters and amides can be formed using methods well known to persons skilled in the art. *See* Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999 (incorporated by reference in page 13 of the specification). Some of the compounds of Formula I which are carboxylic acids, alcohols, or amines also contain ester or amide functionalities. A person having skill in the art would recognize that such compounds could also be derivatized in the same manner as any other carboxylic acid, alcohol, or amine to afford compounds that could be accurately and clearly described as esters or amides of the parent compounds.

Further clarification of the scope of the compounds that comprise esters and amides of the parent compounds of Formula I may be found in the specification, which defines the term "ester" on pages 14-15 and the term "amide" on page 13 in such a way to limit the scope of the variable groups introduced by derivitization of a compound of Formula I. Finally, with respect to the definition of B, which includes $-(CH_2)_j-C(O)OR_4$, where R_4 is H, alkyl, etc, applicant acknowledges that where B is $-(CH_2)_j-C(O)OH$, claim 1 encompasses only those esters of the B group carboxylate that also fall within the limitations of the definition of R_4.

As for the reliance on the fact that specific examples of esters and amides are not disclosed in the specification, applicant believes that the 5th *In re Wands* factor, the presence or absence of working examples, has been overemphasized. 858 F.2d 731 (Fed. Cir. 1988). Here, the level of skill in the pharmaceutical arts is high, formation of esters and amides is a predictable area of the chemical arts, and the scope of the claims relating to esters and amides and the amount of experimentation necessary for their preparation is limited by the definition of "ester" and "amide" in the specification. Accordingly, applicant believes that an analysis of all the relevant *In re Wands* factors shows the rejected claims to be enabled with respect to esters and amides.

Prodrugs

The rejection of prodrugs as lacking enablement appears to be based on the following arguments: (1) that because prodrugs are defined in the specification to include esters and amides of compounds of Formula I, it is not clear whether compounds of Formula I which bear amide or

ester moieties are excluded from being a potential pharmaceutically acceptable prodrug; (2) the specification does not provide any guidance as to where groups such as esters and amides should be placed on the structures of Formula I in order to give a prodrug; (3) in a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a prodrug; and (4) the specification does not contain any working examples of prodrugs.

With respect to the first argument, while it is true that "prodrugs" of compounds of Formula I are defined by the specification to include esters and/or amides, the term "prodrug," encompasses a broader range of derivatives of compounds of Formula I than merely esters or amides. The examiner himself points this out, citing Bundgaard (Design of Prodrugs) for the proposition that prodrugs include polymer-bound prodrugs, acylic precursors of heterocyclic compounds, conjugates of multiple drug molecules, and drugs bound to a carrier via a linker. Furthermore, applicant has never stated that all esters and amides of compounds of Formula I will function as prodrugs. Applicant believes that there is nothing inconsistent in a claim that encompasses compounds that are within the scope of both a functional (prodrugs) and a structural (esters and amides) limitation, even though some of the same compounds may fall within the definition of both limitations.

The second argument, that the specification does not provide any guidance as to where groups such as esters and amides should be placed on the structures of Formula I in order to give a prodrug, gives too little credit to the abilities of a person having ordinary skill in the art. A skilled chemist who seeks to employ a given prodrug strategy, for example one disclosed in the Bundgaard reference cited by the examiner, to make a prodrug of a specific compound of Formula I can readily identify the available sites that can be modified to give a potential prodrug. This is because each prodrug strategy requires specific functional groups for its execution. For example, an amide prodrug would be obtained by derivatizing an amine or a carboxylic acid; an ester prodrug by derivatizing a hydroxyl group or a carboxylic acid; and an acylic prodrug of a heterocyclic compound could only be employed when an appropriate heterocycle is present in the compound of Formula I. Thus, there is no need to disclose in the specification that which would be apparent to one having skill in the art. *In re Wands*. 858 F.2d 731, 735 (Fed. Cir. 1988).

The third argument is that in a clinical trial setting it would require undue experimentation to determine whether a particular compound meets the criteria of a prodrug.

Stated another way, applicant understands this argument to be that a person having ordinary skill in the art could not identify which derivatives of a compound of Formula I have utility as a prodrug without undue clinical experimentation, and therefore prodrugs are not enabled.

Applicant respectfully suggests that it has been improperly assumed that clinical trials are the proper context in which experimentation to determine whether a particular compound meets the criteria of a prodrug occurs. The Federal Circuit has explained that "there is no *per se* requirement for clinical evidence to establish the utility of any invention." *In re Cortwright*, 165 F.3d 1353, 1355 (Fed. Cir. 1999). According to page 27 of the specification, a prodrug is "an agent that is converted into the parent drug *in vivo*." Clinical trials in humans are not required to determine whether *in vivo* conversion of a given prodrug to its parent drug occurs. Such a determination can be made through the use of *in vivo* pharmacokinetic studies in animals. Likewise, the efficacy of produgs can be determined through the use of disease models in animals. The Court of Customs and Patent appeals has upheld the use of *in vivo* data to demonstrate utility where a person of ordinary skill in the art would reasonably believe that *in vivo* or even *in vitro* experimental results identify a pharmacological activity of a compound that is relevant to an asserted pharmacological use. *Nelson v. Bowler*, 626 F.2d 853 (C.C.P.A. 1980). Pharmacokinetic and efficacy studies in animals are a routine experimental step in the pharmaceutical arts. According to the Federal Circuit "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d at 737. Applicant respectfully suggests that the type of experimentation needed to determine whether given derivatives of compounds of Formula I function as prodrugs is not undue.

The fourth and final argument is that the specification does not provide any working examples of prodrugs. According to the Court of Customs and Patent Appeals "[specific working] examples are not required to satisfy section 112, first paragraph." *In re Strahilevitz*, 668 F.2d 1229, 1232 (C.C.P.A. 1982). In *Strahilevitz*, the applicant did not disclose even a single operative embodiment. *Id.* at 1231. The court acknowledged that the claims at issue were extremely broad. *Id.* at 1232. Yet the court reversed the Board's holding of nonenablement, because the invention consisted in combining known prior art techniques. *Id.* at 1234. Likewise, the preparation of prodrugs involves the preparation of compounds of Formula I (which have been found enabled) combined with techniques to derivatize such compounds and analyze them for suitability as prodrugs, both of which techniques are known in the prior art. *See, e.g.,*

Bundgaard (Design of Prodrugs) and Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Accordingly, applicant believes that specific working examples of prodrugs of compounds of Formula I are not required to satisfy 35 USC 112, first paragraph.

Metabolites

The Federal Circuit has defined a metabolite as "the compound formed in the patient's body upon ingestion of a pharmaceutical. The ingested pharmaceutical undergoes a chemical conversion in the digestion process to form a new metabolite compound." *Schering Corp. v. Geneva Pharms., Inc.,* 339 F.3d 1373 (Fed. Cir. 2003). Accordingly, a person having ordinary skill in the art would recognize that pharmaceutically active metabolites compounds of Formula I can be made and used simply by administering compounds of Formula I to an animal or human subject. Furthermore, routine pharmacokinetic experimentation can be performed to identify relevant metabolic intermediates which can then be synthesized using methods known in the art and screened to determine if they are pharmaceutically active.

Solvates

The rejection of solvates of Formula I as lacking enablement is framed in terms of the factors identified by the Federal Circuit in *In re Wands*. 858 F.2d 731 (Fed. Cir. 1988). Briefly, those factors pertaining to enablement are 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or unpredictability of the art, 4) the amount of direction or guidance presented, 5) the presence or absence of working examples, 6) the breadth of the claims, 7) the quantity of experimentation necessary, and 8) the level of skill in the art.

In support of the rejection, it is argued that because the art is unpredictable, there should be enabling disclosure in the specification in the form of working examples, and since there are no working examples, the specification lacks enablement with respect to solvates. However, The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Furthermore, the Federal Circuit has stated that "[a] patent need not disclose what is well known in the art." *In re Wands*. 858 F.2d 731, 735 (Fed. Cir. 1988).

The experimentation required to identify solvates is well known in the art, and involves routine screening of various conditions under which solvates could form. *See e.g.,* K.J. Guillory, Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids, in H.G. Brittain (ed.). Polymorphism in Pharmaceutical Solids, Vol. 95, (1999) pgs. 183-226. The Federal Circuit has stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening" and that even a large number of individual screening operations may be viewed as reasonable (and therefore not undue) by a person skilled in the art. *In re Wands*. 858 F.2d 731, 736-37, 740 (Fed. Cir. 1988). The fact that the art is unpredictable and that screening different conditions for solvate formation is a reliable method of identifying solvates indicates that a person having skill in the art would regard a large amount of such screening as a reasonable amount of experimentation. Furthermore, methods of performing such screening are well known in the art, and therefore there is no need to give detailed direction in the specification.

In further support of the rejection, it is argued that the specification discloses inoperative examples in that working examples of compounds of Formula I were prepared in the presence different solvents, including water, and that no solvates were formed. Applicant respectfully suggests that the nature of these working examples has been mischaracterized. With respect to formation of hydrates, the examples disclosed in the specification indicate that Na_2SO_4, a drying agent, was used to remove trace amounts of water as part of the purification process following a number of the chemical steps involved in the syntheses of exemplary compounds. Thus, there is no evidence from the specification that water was present upon crystallization, or that water was in physical contact with solid compounds of Formula I, a precondition for the formation of a hydrate. Additionally, the examples disclosed in the specification also indicate that the purification process following a number of the chemical steps involved in the syntheses of exemplified compounds involved the removal of solvents. Thus, it is likely that even if solvates formed, they were decomposed during the process of solvent removal. Furthermore, the Federal Circuit has held that the presence of inoperative examples does not necessarily render claims invalid for lack of enablement. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.,* 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Finally, it is argued that the failure of the examples to show solvate formation indicates that there is no evidence that solvates of compounds of Formula I exist. Even if, as the applicant has suggested, the conditions used to synthesize the exemplified

compounds were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates, a reference cited by the examiner indicates that "approximately one-third of [] pharmaceutically active substances are capable of forming crystalline hydrates." Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26 (2001). Thus, since the pending claims encompass a large number of individual compounds, and the claimed pharmaceutically acceptable solvates include solvents other than water, the prior art indicates that there is a substantial likelihood of success in forming solvates of at least some of the compounds of Formula I.

General Rejections of Claims 51-53, 57-61, and 65

Several general and specific arguments were made in support of the rejection of claims 51-53, 57-61, and 65 under 35 USC 112, first paragraph. Because it was not precisely specified which claims are being rejected for some of the reasons given, these arguments will be addressed first, followed by the arguments directed towards specific claims.

In support of the rejection, it is first argued that the specification does not enable one skilled in the art to use the claimed compounds as PPAR regulators. It is also claimed that no results in the PPAR binding activity assays disclosed on pages 21-22 are provided for any of the exemplified compounds. Applicant respectfully suggests that this is not the case. Exemplified compounds were evaluated in a cell-based assay to determine their human PPAR activity, the results of which are disclosed on pages 48-51 of the specification.

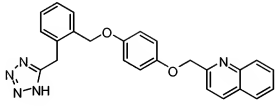
It is further argued that the varying results obtained for the tested compounds indicate that the relevant area of receptor activity is highly structure specific and unpredictable. However, applicant respectfully points out that even if that is the case, applicant has disclosed assays and methods by which the claimed compounds can be routinely screened to evaluate their PPAR binding affinity. Because the PPAR binding activity can be determined through routine experimentation, a person having skill in the art has no need to be able to predict activity based on structure in order to practice the claimed invention.

It is also argued that there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being predictive of success in the area of regulating PPAR. In support of this argument, examiner cites a PubMed abstract summarizing Fayer et al., J. Clin. Pharmacol. 41; 305 (2001), stating that factors other than plasma drug

concentrations and potency of in vitro enzyme inhibition are important when extrapolating in vitro models of CYP inhibition to predict in vivo drug-drug interactions between RG 12525 (2-[[4-[[2-(1H-tetrazole-5-ylmethyl)phenyl]methoxy]phenoxy]methyl] quinolone), a novel PPAR-gamma agonist, and midazolam, a CYP3A4 substrate.

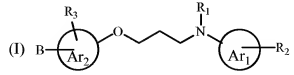
With respect to the Fayer reference, applicant notes that it is directed to an extrapolation of *in vitro* data predicting that administration of RG 12525 would have an effect on the metabolism of midazolam by CYP3A4 *in vivo*, and that no effect was found in the *in vivo* studies. Applicant respectfully suggests that the Fayer reference makes no claim about the predictive value or lack thereof of *in vitro* results in PPAR binding assays to *in vivo* PPAR modulating activity. PPAR-modulating activity and the ability of PPAR-modulators to effect specific biological results is the property at issue in the objected-to-claims. Therefore, the Fayer reference does not support the assertion that the art does not recognize *in-vitro* screening tests as being predictive of success in the area of regulating PPAR.

With respect to the Fayer reference, applicant further notes that RG 12525 is a distinct chemical entity from the claimed compounds. The structure of RG 12525 is as follows:



RG 12525

Compared to the claimed compounds of Formula I:



(I)

wherein Ar_1 is pyrimidine, it is clear that there are significant structural differences between RG 12525 and the claimed compounds. For example, RG 12525 does not possess the following structural features of the claimed compounds of Formula I: a tertiary amine, a pyrimidine ring system, an internal n-propylene group, etc. Likewise, the claimed compounds of Formula I do

not possess the following structural features of RG 12525: a quinoline ring system, a –O-Ph-O- linker, etc. Since RG 12525 differs structurally from the claimed compounds, and pharmacokinetic and CYP inhibition properties are structure-dependent, it would be improper to infer that the claimed compounds would show an effect on the metabolism of midazolam by CYP3A4 using the *in vitro* methods of the Fayer reference, or that the such *in vitro* results would lack predictive value for the compounds of the claimed methods.

Finally, it is argued that there is no evidence on record which demonstrates that *in vitro* PPAR binding assays such as those disclosed in the specification are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR. Applicant respectfully suggests that this is not the case, and points to pages 1-3 and 23-25 of the specification, which cite numerous references correlating the regulation of PPAR with existing and potential treatments of numerous diseases. For example, correlations between *in vivo* efficacy and activity in PPAR binding assays for given compounds have been established - see page 22 of the specification, citing *J. Biol. Chem.*, 1995, 270, 12953-6 for the proposition that an antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma.

For the reasons stated above, it is respectfully suggested that *in vitro* PPAR binding assays such as those disclosed in the specification are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR and it is requested that the rejection be withdrawn.

A Method of Modulating a PPAR Function (Claims 51-52)

Claims 51-52, which recite "a method of modulating a PPAR function" were rejected because, it is argued, "the term 'modulating' generally encompasses blocking, activating, partial blocking and partial activating" and that none of the compounds were shown to have all these (revolutionary) properties. Applicant respectfully directs examiner's attention to the definition of the term "modulate" on pages 20-21 of the specification, which states:

> The term "modulate" refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the

> activity of a PPAR. The term "modulate" also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner. A modulator may increase the probability that such a complex forms between the PPAR and the natural binding partner, may increase or decrease the probability that a complex forms between the PPAR and the natural binding partner depending on the concentration of the compound exposed to the PPAR, and or may decrease the probability that a complex forms between the PPAR and the natural binding partner.

Applicant respectfully notes that nowhere in the specification is it suggested that any of the claimed compounds have the ability to block, activate, partially block and partially activate a PPAR function at the same time. According to the specification, modulation of PPAR function by a single compound at a given concentration may either activate or inhibit of a PPAR, or "increase[e] or decreas[e] the probability that a complex forms between a PPAR and a natural binding partner" The rejection appears to be based on a definition of the term "modulate" that is at odds with the definition provided in the specification. The Federal Circuit has stated that "[c]laims must be read in view of the specification, of which they are a part." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). Therefore, applicant respectfully suggests that the examiner's proposed definition of the term "modulating" is not an appropriate basis for a rejection of claims 51-52 under 35 USC 112, first paragraph, and requests that the rejection be withdrawn.

It is further argued that "the specification did not provide any competent tests or data to establish that the compounds have the claimed 'calcium sensing receptor modulating activity.'" Applicant respectfully notes that since calcium sensing receptor modulating activity was not in fact claimed, the lack of such tests or data is not relevant to any of the claims currently pending.

Claims Rejected as "Reach-through" Claims (Claims 53, 57, 59-61, and 65)

Claims 53 and 57, which recite "a method of inhibiting the formation of adipocytes in a mammal," 59 and 65, which recite "a method of treating a PPAR-modulated disease," 60, which recites "a method of treating a metabolic disorder or condition," and 61, which recites "a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia,

metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury," were rejected because, it is argued, claims 53, 57, 59-61, and 65 are "reach through" claims. It is stated that "[r]each through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure."

Applicant respectfully suggests that, in characterizing claims 53, 57, 59-61, and 65 as "reach through claims" claims 53, 57, 59-61, and 65 have not been read as a whole. Claim 53 reads: "A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 1 to the mammal." Claim 57 reads: "A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 50 to the mammal." Claims 53 and 57 do not encompass a method of inhibiting the formation of adipocytes in general. Rather, they encompass a method by which the formation of adipocytes is inhibited by administering a therapeutically effective amount of a compound of Formula I (claim 1) or Formula III (claim 50). As currently pending, claim 59 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 65 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of the compound of Claim 50 to the patient." Claims 59 and 65 do not encompass a method of treating a PPAR-modulated disease or condition in general. Rather, they encompass a method by which a PPAR-modulated disease or condition is treated by administering a therapeutically effective amount of a compound of Formula I (claim 1) or Formula III (claim 50). As currently pending, claim 60 reads: "A method of treating a metabolic disorder or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 60 does not encompass a method of treating a metabolic disorder or condition in general. Rather, it encompasses a method by which a metabolic disorder or condition is treated by administering a therapeutically effective amount of a compound of

Formula I (claim 1). As currently pending, claim 61 reads: "A method of treating a disease ~~is~~ selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 61 does not encompass a method of treating the listed diseases in general. Rather, it encompasses a method by which certain diseases are treated by administering a therapeutically effective amount of a compound of Formula I (claim 1).

Therefore, claims 53, 57, 59-61, and 65 are not "reach through claims" as examiner has defined that term. The fact that claims 53, 57, 59-61, and 65 are not "reach though claims" is further illustrated by comparison with the claims at issue in *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). In *Univ. of Rochester*, the Federal Circuit rejected "reach through" claimed methods for inhibiting PGHS-2 activity in a human host comprising administering a compound, when the specification did not disclose the chemical structure of any such compound. *Id.* Here, the structures of the compounds to be administered are disclosed to be of Formula I (claims 53 and 59-61) and Formula III (claim 57 and 65). Applicant therefore suggests that the written description and enablement requirements under 35 USC 112, first paragraph have been met with respect to claims 53, 57, 59-61, and 65, and requests that the rejection be withdrawn.

Method of Treating a PPAR-Modulated Disease (Claims 59 and 65)

Claims 59 and 65, drawn to "a method of treating a PPAR-modulated disease or condition" were rejected as lacking enablement because they include disorders that are known to exist as well as those that may be discovered in the future, and, therefore, the claims are extremely broad. Applicant respectfully suggests that this is not the case. Although it is possible that diseases currently exist that are not known to be modulated by PPAR, it is respectfully suggested that a prima facie case has not been stated showing why that means that the claimed methods for their treatment are not enabled. Applicant notes that the no evidence has been cited in support of the assertion that a significant number of unknown PPAR-modulated diseases will

be discovered in the future or why the treatment of such diseases are not enabled by the specification. After all, one does not have to know that a disease is modulated by PPAR in order to treat it through administration of an appropriate PPAR modulator. Applicant therefore requests that the rejection under 35 USC 112, first paragraph, be withdrawn.

A method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury (Claim 61)

Claim 61, drawn to "a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury" was rejected as lacking enablement because, for example, "atherosclerosis is a common form of arteriosclerosis associated with the formation of artheromas which are deposits of yellow plaques containing cholesterol, lipids, and lipophages within the intima and inner media of arteries" and that "[t]his results in a narrowing of the arteries, which reduces the blood and oxygen flow to the heart and brain as well as to other parts of the body and can lead to a heart attack, stroke, or loss of function or gangrene of other tissues." It is not stated why the fact that atherosclerosis is a common form of arteriosclerosis, and that atherosclerosis results in the narrowing of the arteries, which can subsequently lead to heart attack, stroke, or loss of function or gangrene of other tissues means that claim 61 lacks enablement. Therefore, applicant respectfully suggests that examiner has failed to state a prima facie case of lack of enablement of claim 61 and it is requested that the rejection be withdrawn.

For the reasons stated above, it is respectfully suggested that the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I; a method of modulating a PPAR function; a

method of inhibiting the formation of adipocytes in a mammal; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally; and a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury, and it is requested that the rejection be withdrawn.

Response to Rejections Under 35 USC 112, Second Paragraph

Claims 1-17, 19-36, 48-49, 51-53, 58-61, and 66-69 were rejected under 35 USC 112, second paragraph. The four reasons are cited in support of the argument that these claims are indefinite. Claims 14-17 and 58 are cancelled. It is respectfully submitted that Claims 1-13, 19-36, 48-49, 51-53, 59-61, and 66-69 were not properly rejected for the following reasons.

The first reason cited is that the terms "ester" or "amide" as used in claim 1 to describe derivatives of compounds of Formula I. It is stated that because the definitions of various substituent groups in Formula I are such that Formula I encompasses free acids as well as esters and amides, it is not clear what the difference is between the substituent groups recited and an ester or amide of a compound of Formula I. Applicant respectfully suggests that this is not the case. An ester can be formed from an alcohol or carboxylic acid. Likewise, an amide can be formed from an amine or carboxylic acid. As defined in claim 1, compounds of Formula I include carboxylic acids, alcohols, and amines, from which derivatives such as esters and amides can be formed using methods well known to persons skilled in the art. *See, e.g.,* Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999 (incorporated by reference in page 13 of the specification). Some of the compounds of Formula I which are carboxylic acids, alcohols, or amines also contain ester or amide functionalities. A person having skill in the art would recognize that such compounds could also be derivatized in the same manner as any other carboxylic acid, alcohol, or amine to afford compounds that could be accurately and clearly described as esters or amides of the parent compounds.

Furthermore, with respect to the definition of B, which includes $-(CH_2)_j-C(O)OR_4$, where R_4 is H, alkyl, etc, applicant acknowledges that where B is $-(CH_2)_j-C(O)OH$, claim 1

encompasses only those esters of the B group carboxylate that also fall within the limitations of the definition of R_4.

Therefore, applicant respectfully suggests that the terms "ester" and "amide" have a clear meaning to persons skilled in the relevant art and requests that the rejection of claim 1 under 35 USC 112, second paragraph be withdrawn. Claims 2-13, 19-20, 22-36, 51-53, and 66-69 depend from claim 1 and are as originally presented. Claims 21, 48-49, and 59-61 depend from claim 1 and are currently amended.

The second reason cited in rejecting claim 21 under 35 USC 112, second paragraph is that claim 21 recited the improper claim language "any of claim 20". In accordance with the examiner's suggestion, claim 21 has been amended to remove the term "any of". Accordingly, applicant requests that the rejection of claim 21 under 35 USC 122, second paragraph be withdrawn.

The third reason cited in rejecting claim 51 under 35 USC 112, second paragraph is that claim 51 recites the steps "and monitoring a change in cell type, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner". It is stated that this language is indefinite and that "[t]he specification does not provide any help." However, applicant respectfully directs the examiner to the Detailed Description of the Invention, Section II, pgs. 19-22 of the specification, which defines the terms "cell phenotype," "cell proliferation," and "monitoring" and describes methods of monitoring the activity and binding of PPAR. Because the stated reason for rejecting claim 51 as indefinite appears to the applicant to be based on the fact that the specification does not provide guidance as to the meaning of the claim language objected to, and because the applicant has pointed out such guidance in the specification, applicant requests that the rejection of claim 51 under 35 USC 112, second paragraph, be withdrawn. Claim 52 depends from claim 1 and is as originally presented.

The fourth reason cited in rejecting claim 58 under 35 USC 112, second paragraph is that claim 58 recites "A method of treating a disease comprising identifying a patient in need thereof" without specifically providing which disease is intended. Claim 58 has been cancelled. Claims 59-61, which depended from claim 58, have been rewritten in independent form. Applicant respectfully suggests that claims 59-61 as currently pending are in condition for allowance.

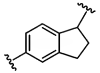
Response to Rejections Under 35 USC 102

Claims 1, 14-17, 19-29, 32-36, 51-53, 58-61, and 66 were rejected under 35 USC 102(e) as being anticipated by Cantin et al. (WO 04/058174).

It is noted with appreciation that the currently pending claims 28-36, and 70 (as originally presented) and claims 38, 66, and 72 (not amended but for bringing into conformance with the restriction requirement) have been found novel in light of Cantin et al.

It is argued that compounds of structural Formula (I) and the corresponding species of examples 282-289 and 292-300 disclosed in Cantin et al. anticipate the specified claims.

It is respectfully submitted that claims 19-21 have been improperly rejected under 35 USC 102(e) as being anticipated by Cantin et al. Claims 19-21 depend alternatively from claims 4 or 5, which are drawn to compounds where Ar_2 is phenyl (claim 4) or napthyl (claim 5). In the structures disclosed in Cantin et al., the group analogous to Ar_2 is:



Because the group analogous to Ar2 in the structures disclosed by Cantin et al. is neither phenyl or napthyl, as in claims 19-21 of the instant application, it is requested that the rejection of these claims under 35 USC 102(e) be withdrawn.

Claim 1 has been amended to remove the cited compounds from its scope, and is now drawn to compounds of the Formula (I), wherein j is 0 when Ar_2 is a bicyclic or tricyclic carbocyclic ring structure. Cantin et al. discloses compounds where Ar2 is a bicyclic carbocyclic ring structure and j is 1. Therefore, it is respectfully submitted that the reference Cantin et al. (WO 04/058174) no longer anticipates the claim.

Claims 22-29, 32-36, 51-53, 59-61, and 66 depend from claim 1 and thus no longer read on the compounds disclosed by Cantin et al.

Claims 14-17 and 58 have been cancelled.

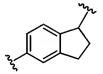
Response to Rejections Under 35 USC 103

Claims 1, 14-17, 19-29, 32-36, 51-53, 58-61, and 66 were rejected under 35 USC 103(a) as obvious in light of Cantin et al. (WO 04/058174).

It is noted with appreciation that the currently pending claims 28-36, and 70 (as originally presented) and claims 38, 66, and 72 (not amended but for bringing into conformance with the restriction requirement) have been found nonobvious in light of Cantin et al.

The finding of prima facie obviousness was based on (1) the fact that the generic group of pyrimidine compounds disclosed by Cantin et al. (formula (I) in page 2 and examples 282-289 and 292-300) embraces the instantly claimed compounds. Furthermore, *In re Susi*, 440 F.2d 442 (1971) is cited for the proposition that a prior art reference that disclosed a genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus.

As originally presented, claims 19-21 depend alternatively from claims 4 or 5, which are drawn to compounds where Ar_2 is phenyl (claim 4) or napthyl (claim 5). Thus, they do not claim species falling within the genus disclosed by Cantin et al., wherein the group analogous to Ar_2 is:



Thus, it is respectfully suggested that the stated grounds for rejection under 35 USC 103 do not apply to claims 19-21, and applicant requests that the rejection to these claims be withdrawn.

The definition of j in claim 1 when Ar_2 is a bicyclic carbocyclic ring structure has been amended such it no longer encompasses compounds having the structural features disclosed in Cantin et al. (formula (I) in page 2 and examples 282-289 and 292-300). Claims 22-29, 32-36, 51-53, 58-61, and 66 depend from claim 1. Since these claims no longer read on species falling within the genus disclosed by Cantin et al., it is respectfully suggested that the stated grounds for rejection under 35 USC 103 no longer applies to them, and the applicant therefore believes that claims 1, 22-29, 32-36, 51-53, 59-61, and 66 are nonobvious in light of Cantin et al. and it is proper to withdraw the rejection.

Claims 14-17 and 58 are canceled.

In light of the above, reexamination and reconsideration of the application under 37 C.F.R. § 1.114 is requested. Allowance of the pending claims at an early date is solicited. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the case. Please continue to direct all correspondence to Global Patent Group at P.O. Box 38100 in St. Louis, MO 63138.

Respectfully submitted,

/ Dennis A. Bennett/

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